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**Declarations under Rule 4.17:**

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(54) Title: IMPROVEMENTS IN OR RELATING TO ORAL CHLORHEXIDINE FORMULATIONS

(57) Abstract: An oral chlorhexidine formulation is provided comprising one or more chlorhexidine salts, together with other optional active ingredients such, for example, as fluoride. Aspartame, and other optical flavouring agents such, for example, as peppermint oil are used to mask the bitterness of the chlorhexidine, whilst a combination of excipients is used which preserves the solubility and stability of the chlorhexidine and other optional active ingredients in water. The oral formulation according to the invention preserves more than 90 % of the label strength of chlorhexidine salts when dispersed in water.

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**Improvements in or relating to oral chlorhexidine formulations**

The present inventions relates to improvements in or relating to chlorhexidine formulations and, in particular, provides a novel chlorhexidine formulation that is adapted to mask the unpleasant, bitter flavour of chlorhexidine when taken orally, whilst maintaining the stability and solubility of chlorhexidine in water.

Chlorhexidine salts, such for example, as chlorhexidine gluconate, are widely used in oral hygiene products including mouth washes and the like for their anti-bacterial properties. In particular, chlorhexidine salts are used in oral products for the treatment of gingivitis and the prevention of plaque. However, chlorhexidine suffers from the disadvantage that it has an extremely bitter taste which most people find unacceptable

Accordingly, numerous attempts have been made in the art to mask the bitterness of chlorhexidine in oral products. For example, GB 2035084A discloses oral products, such as dentifrice and mouthwashes, comprising chlorhexidine and a flavouring mixture comprising at least one of essential citrus oils (other than lime oil), synthetic equivalents thereof, benzyl salicylate, and anisic alcohol as a bitterness/masking constituent. US 4601900A discloses a mouthwash comprising chlorhexidine and xylitol to cover the bitter taste of the chlorhexidine.

EP 0306455A1 describes the use of cyclodextrin to form complexes of bis-bi-guanido hexane compounds such as chlorhexidine for use in anti-bacterial oral compositions. According to EP 0306455A1, chlorhexidine complexes of bis-bi-guanido hexane compounds act to increase the solubility of the chlorhexidine or derivative for making such compounds easier to incorporate in aqueous-based anti-bacterial compositions. Further, by virtue of complexing, the bitter taste of the chlorhexidine is effectively masked. In addition, it has been found that the bio-availability of the chlorhexidine can be increased by complexing with cyclodextrins. Optionally, the oral compositions of EP0306455 A1 may including auxiliary sweeteners selected from water-soluble sweetening agents such as monosaccharides, di-saccharides and polysaccharides, water soluble-artificial sweeteners such as the soluble cyclamate salts and the like, and dipeptide taste sweeteners such as L-phenylalanine ester and the like.

In Braz. Dent. J., 2000; 11(1): 29-34 (ISSN 0103-6440) Cury, *et al* disclose an oral chlorhexidine gel containing aspartame as a sweetener.

Aspartame sweetening agents (aspartyl phenylalanine methyl ester, and its related compounds aspartyl phenylalanine ethyl ester, aspartyl phenylalanine n-propyl ester,

aspartyl phenylalanine isopropyl ester, and aspartyl phenylalanine tert-butyl ester) are well known as intense sweetening agents, following their invention by Schlatter in 1965. The synthesis of aspartame sweetening agents is disclosed in US 3492131A to Schlatter, the contents of which are incorporated herein by reference.

Another problem with chlorhexidine and its salts is that they are highly reactive leading to instability, particularly at concentrations of the kind that are normally used for anti-bacterial oral preparations.

Accordingly, an object of the present invention is to provide a novel oral chlorhexidine formulation.

Another object of the present invention is to provide an oral chlorhexidine composition which masks the bitterness of chlorhexidine.

Yet another object of the present invention is to provide a dispersible oral chlorhexidine formulation which is susceptible of being formed in to tablets for oral administration.

Yet another object of the present invention is to provide oral chlorhexidine formulation with good stability.

Yet another object of the present invention is to provide oral chlorhexidine formulation with good solubility.

Yet another object of the present invention is to provide a chlorhexidine formulation for oral administration which may include further active ingredients, with good solubility and stability of such further active ingredients.

According to one aspect of the present invention therefore there is provided an oral chlorhexidine formulation that is adapted to mask the bitterness of chlorhexidine, said oral formulation comprising one or more chlorhexidine salts, and optionally one or more other active ingredients, a bitterness masking amount of an aspartame sweetening agent, and excipients comprising microcrystalline cellulose and a non-active, chlorhexidine-compatible, water-soluble polyoxyethylene glycol, and optionally one or more other flavour enhancing agents.

The chlorhexidine formulation in accordance with the present invention can be formed into compressed, dispersible tablets, and it has been found that when such tablets are dispersed in distilled water, the chlorhexidine salt is still as active as in a simple solution in distilled water. Thus, the solubility and stability of the chlorhexidine is

substantially maintained, and the aspartame sweetening agent serves to mask the bitterness of the chlorhexidine.

In the oral chlorhexidine formation of the present invention, said one or more chlorhexidine salts do not form a complex with other chemical species such, for example, as chlorhexidines as described in EP 0306455 A1.

Any suitable chlorhexidine salt may be used, including chlorhexidine gluconate. In some embodiments, chlorhexidine acetate may be used.

Any aspartame sweetening agent, or combination of aspartame sweetening agents may be used in the chlorhexidine formulation in accordance with the present invention, but in some embodiments aspartyl phenylalanine methyl ester which is commercially available under the trade name "NutraSweet" may be employed. Advantageously, aspartame sweetening agents are chemically compatible with chlorhexidine, and do not lose their sweetness in water prior to use. Preferably the oral chlorhexidine formulation in accordance with the present invention comprises at least about 14% wt. of aspartame, and in some embodiments about 14 to 18% wt. aspartame may be used.

Microcrystalline cellulose is an oral tablet excipient and diluent that is directly compressible, with lubricant and disintegrant properties. Suitably, the chlorhexidine formulation according to the present invention comprises an amount of microcrystalline cellulose that is adapted to render said chlorhexidine salts, said one or more other optional active ingredients, and said aspartame sweetening agent, directly compressible into a tablet of a suitable size, having sufficient hardness, which will disperse readily in water to release the chlorhexidine and other optional active ingredients and aspartame sweetening agent. Microcrystalline cellulose is insoluble in the formulation, but desirably has a "non-gritty" sensation to the mouth.

Suitably the oral chlorhexidine formulation according to the present invention comprises up to about 79% wt. microcrystalline cellulose, and in some embodiments 72 to 79% wt. microcrystalline cellulose may be employed.

Said non-active, chlorhexidine-compatible, water-soluble polyoxyethylene glycol is used as a tablet lubricant. In some embodiments, said polyoxyethylene glycol may comprise any polyoxyethylene glycol having a molecular weight that is suitable for incorporation in a dispersible tablet formulation. In some embodiments, polyoxyethylene glycol $[H-(OCH_2CH_2)_n-OH]$ having an average molecular weight of about 4000, which is readily soluble in water, aiding tablet dispersion, is used. Although during tablet

formation, some powder may adhere during compression to punch faces, it may be readily removed. "Macrogol 4000" which is a commercially-available form of polyoxyethylene glycol 4000, may be used in some embodiments. Alternatively, a polyoxyethylene glycol having an average molecular weight in the range 5000-7000, preferably 5500-6500, e.g. about 6000, may be used. The oral chlorhexidine formulation in accordance with the present invention may comprise about 2 to 5.7% wt polyoxyethylene glycol.

In some embodiments, the oral chlorhexidine formulation according to the present invention may comprise one or more other flavour-enhancing agents. In some embodiments, peppermint oil may be used as a flavour-enhancing agent. The concentration of said other flavour-enhancing agents used in the formulation of the present invention may be chosen to avoid problems of tablet cohesion or bulk powder flow during compression. In addition, the amount chosen should be acceptable to humans, including children, and suitably up to about 0.3% wt of peppermint oil may be used.

The present invention thus comprehends a sweetened, flavoured approach using selected compatible excipients, for preparing a compressed, dispersible tablet of chlorhexidine in which the bitterness of chlorhexidine is masked whilst maintaining its solubility and stability.

Suitably, said one or more chlorhexidine salts are present in the formulation in an anti-bacterial amount. In some embodiments, the amount of chlorhexidine salt or salts incorporated in the formulation according to the present invention may be sufficient to provide a dispersion of at least 0.05% w/v when dispersed in about 10ml of water. In some embodiments, the amount of chlorhexidine salt or salts incorporated in the formulation may provide a dispersion of about 0.14% w/v in 10mls of water.

The oral chlorhexidine formulation according to the present invention may comprise 4.3 to 5.6% wt chlorhexidine.

As mentioned above, the formulation in accordance with the present invention may comprise one or more other active ingredients such, for example, as agents for the prevention of dental caries, e.g. a fluoride. In some embodiments, the oral chlorhexidine formulation in accordance with the present invention may comprise sodium fluoride, and it has been found that the solubility and stability of fluoride is substantially unaffected by the formulation of the present invention. Suitably, the formulation according to the present invention may comprise an amount of fluoride sufficient to provide a 0.05% w/v solution

of fluoride when dispersed in about 10 mls of water. In some embodiments, the formulation may comprise about 1.4 to 2% wt sodium fluoride.

In another aspect of the present invention there is provided an oral chlorhexidine formulation comprising:

1.4 % wt. sodium fluoride

4.3 % wt. chlorhexidine acetate

14.3 % wt. aspartame

74.0-74.3 % wt. microcrystalline cellulose

5.7 % wt. polyoxyethylene glycol 4000

0.0-0.3 % wt. peppermint oil.

In yet another aspect of the present invention there is provided an oral chlorhexidine formulation comprising:

2.0% wt sodium fluoride

5.6% wt chlorhexidine acetate

18.0% wt aspartame

72.4% wt microcrystalline cellulose

2.0% wt polyoxyethylene glycol 4000.

In accordance with yet another aspect of the present invention there is provided a method of making an oral chlorhexidine formulation in accordance with the present invention which comprises mixing one or more chlorhexidine salts, one or more other optional active ingredients, and a non-active, chlorhexidine-compatible, water-soluble polyoxyethylene glycol with microcrystalline cellulose and thereafter milling the mixture to form a uniform powder.

Said powder may be compressed, for example, using a conventional tableting machine, to form tablets of the formulation. During tableting, the punch faces of the tableting machine may be regularly cleaned in order to remove any power adhesion to the punch faces.

In some embodiments, the mixutre of microcrystalline cellullose, chlorhexidine salt(s), other optional active ingredients and polyoxyetheylene glycol may be mixed with a mixture of microcrystalline cellulose and one or more other flavour-enhancing agents such, for example, as peppermint oil, prior to milling.

The chlorhexidine formulation of the present invention may be administered in tablets or powder form, or as a chewing gum, lozenge, pastel, toothpaste or oral gel. When

used in powder form the formulation of the present invention may be metered into hard gelatine capsules or other suitable containers for the dispersal of the powder in water.

Following is a description by way of example only of embodiments of the present invention.

**Description 1: Procedure for making powder formulation**

The following procedure is suitable for making powder formulations of the following examples of the present invention, and the comparative examples.

Measured amounts of sodium fluoride, chlorhexidine acetate and a polyoxyethylene glycol tablet lubricant (e.g. Macrogol 4000 or Macrogol 6000) are weighed in separate, tared, large weighing boats. The weighed powders are then transferred to a large mortar where they are mixed using a pestle for about 10 minutes, scraping down with a spatula at approximately 2 minute intervals.

An amount of microcrystalline cellulose is weighed in a tared, stainless steel container, and then added to the contents of the mortar, which are then mixed again for about 10 minutes, scraping down at 2 minute intervals as before. The contents of mortar are then transferred to a ball mill 'pot', which is charged with stainless steel balls.

An amount of aspartame is weighed in a separate tared stainless steel container and then added to the contents of the pot.

Optionally, a further amount of microcrystalline cellulose is weighed in the tared stainless steel container used previously for weighing microcrystalline cellulose, and is then divided into portions. One portion is added to the mortar used previously.

A small amount of a flavour agent is then weighed in a tared small weighing boat and, is subsequently added to the one portion of microcrystalline cellulose in the mortar. The other portion of microcrystalline cellulose is used to absorb any residues of flavour agent in the small weighing boat and it is then transferred to the mortar with a small spatula.

The contents of the mortar are then mixed for about 4 minutes with the pestle, scraping down at approximately 2 minutes intervals with the spatula.

The contents of the mortar are then transferred to the ball mill pot.

This optional procedure can be omitted if no flavouring agent is used.

The lid of the pot is then secured, ensuring that the gasket is in position to prevent powder leakage during milling.

The pot is then placed on Pascall rollers, and the mixture is milled for about 1 hour.

After milling, the milled powder and balls are separated using a 1000μ stainless steel sieve which is gently agitated until all the powder is transferred to a stainless steel tray beneath the sieve.

Thereafter, the milled powder is checked visually, and samples may be taken for quality control.

**Description 2: Procedure for tableting a powder**

A blended powder prepared as described above is formed into tablets using a conventional Manesty F3 tableting machine using 10mm standard concave punches and die. The blended powders, prepared as described above, are scooped gently under dust extraction into the tableting machine feed hopper. The tableting machine is then operated at slow speed, and during compression, the produced tablets are observed for any discolouration, e.g. black specks on their surfaces.

Formulations using polyoxyethelene glycol as a tablet lubricant may exhibit powder adhesion to the machine's punch faces, accordingly, every approximately 10 minutes, the upper and lower punch faces are cleaned using industrial methylated spirits and thoroughly dried, before restarting the machine.

**Example 1**

Using the powder milling and tableting procedures described above, tablets of chlorhexidine acetate and sodium fluoride are produced having the following composition:

| | |
|---|---|
| Sodium fluoride | 5mg |
| Chlorhexidine acetate | 5mg (1mg overage) |
| Aspartame | 50mg |
| Microcrystalline cellulose (Avicel 101) | 259mg |
| Macrogol 4000 | 20mg |
| Peppermint oil | 1mg |
| | --- |
| | 350mg |

Approximately 3000 tablets (theoretical yield) are made using 15g of sodium fluoride, 45g chlorhexidine acetate, 150g aspartame, 777g microcrystalline cellulose, 60g Macrogol 4000 and 3g peppermint oil. During preparation of the powder, 400g of the microcrystalline cellulose are mixed initially with the sodium fluoride, chlorhexidine acetate and aspartame, and 377g are mixed with the peppermint oil, and then subsequently

added to the microcrystalline cellulose, chlorhexidine acetate, sodium fluoride, Macrogol 4000 mixture.

A table of example 1 when dispersed in 10ml of distilled water, provided active ingredients chlorhexidine acetate 0.14% w/v and sodium fluoride 0.05% w/v without bitter taste, and the chemical structure was stable with good stability of the two active ingredients. Validation of the formula was carried out using established methods. HPLC was used to verify the final concentration of chlorhexidine acetate and an ion-selective electrode method was used to verify the fluoride concentration. The masking of the bitter taste was carried out on a minimum of three healthy individuals who did not have any known disability in tasting.

The percentage of label strength of chlorhexidine acetate when dissolved in 10ml of distilled water was found to be (2 tablets tested): 99.5% and 100.6%.

**Example 2**

Oral chlorhexidine tablets were made using the procedures described above with the following composition:

| | |
|---|---|
| Sodium fluoride | 5mg |
| Chlorhexidine acetate | 40mg |
| Aspartame | 45mg |
| Microcrystalline cellulose | 181mg |
| Macrogol 4000 | 5mg |
| | --- |
| | 250mg |

The percentage label strength of chlorhexidine acetate when a tablet was dispersed in 10ml of distilled water was found to be (two tablets tested) 94.6% and 95.7%.

**Comparative Examples 3 to 6**

Using the procedures described above, tablets comprising the following formulations were made:

**Table 1**

| **Comparative Example:** | **3** | **4** | **5** | **6** |
|---|---|---|---|---|
| **Ingredients** | **Amounts /mg** | | | |
| Sodium fluoride | 5 | 5 | 5 | 5 |
| Chlorhexidine acetate | 14 | 14 | 14 | 14 |

| | | | | |
|---|---|---|---|---|
| Aspartame | 30 | 30 | 45 | 45 |
| Strawberry flavour powder | 10 | 10 | - | - |
| Microcrystalline cellulose | 169 | 198 | 193 | 227 |
| Sodium starch glycollate | 10 | - | - | - |
| Magnesium stearate | 2 | 3 | 3 | - |
| Stearic acid | - | - | - | 9 |

The percentage of label strength of chlorhexidine acetate for each of Comparative Examples 3 to 6, when one tablet was dispersed in 10ml of distilled water, is shown in Table 2:

**Table 2**

| **Formulation** | **% Label strength of chlorhexidine acetate when one tablet dispersed in 10mls distilled water** | |
|---|---|---|
| | **1** | **2** |
| Example 1 | 99.5% | 100.6% |
| Example 2 | 94.6% | 95.7% |
| Comparative Example 3 | 51.5% | 55.0% |
| Comparative Example 4 | 89.1% | 89.5% |
| Comparative Example 5 | 81.3% | 81.6% |
| Comparative Example 6 | 75.5% | 77.6% |

As can be seen from the foregoing, the chlorhexidine formulations in accordance with the present invention provided significantly enhanced label strength chlorhexidine acetate when dispersed in water as compared with the Comparative Examples 3 to 6. Furthermore, the aspartame and optional flavouring agent included in the oral formulation of the present invention masked the unpleasant taste of chlorhexidine. Although the substances aspartame, microcrystalline cellulose, polyoxyethylene glycol and peppermint oil as flavouring agent are well known in the art for their individual activities, the combination of these ingredients to provide an oral formulation for administration of chlorhexidine salts is unexpectedly advantageous in preserving the stability and solubility of chlorhexidine salts in aqueous dispersion whilst masking the bitterness of the

chlorhexidine. As evidenced above, other excipients such as sodium starch glycollate (disintegrant) magnesium stearate and stearic acid (lubricants) are unsuitable.

**Claims**

1 An oral chlorhexidine formulation that is adapted to mask the bitterness of chlorhexidine, said oral formulation comprising one or more chlorhexidine salts and optionally one or more other active ingredients, a bitterness masking amount of an aspartame sweetening agent, an excipient comprising microcrystalline cellulose and a non-active, chlorhexidine-compatible, water-soluble polyoxyethylene glycol, and optionally one or more flavouring agents.

2 An oral chlorhexidine formulation as claimed in claim1, wherein said polyoxyethylene glycol comprises polyoxyethylene glycol 4000 or polyoxyethylene glycol 5000-7000.

3 An oral chlorhexidine formulation as claimed in claim 1 or claim 2, wherein said one or more chlorhexidine salts are present in said formulation in an antibacterial amount.

4 An oral chlorhexidine formulation as claimed in claim 3, comprising an amount of chlorhexidine salt or salts to provide a dispersion of at least about 0.05 % w/v when dispersed in about 10 ml water.

5 An oral chlorhexidine formulation as claimed in any preceding claim, comprising about 4.3-5.6 % wt. chlorhexidine salt or salts

6 An oral chlorhexidine formulation as claimed in any preceding claim, wherein said one or more chlorhexidine salts comprise chlorhexidine acetate.

7 An oral chlorhexidine formulation as claimed in any preceding claim, further comprising a fluoride for the prevention of dental caries.

8 An oral chlorhexidine formulation as claimed in claim 7, wherein said fluoride comprises sodium fluoride.

9 An oral chlorhexidine formulation as claimed in claim 8, comprising an amount of sodium fluoride that is adapted to provide a 0.05 % w/v solution of fluoride when dispersed in about 10 ml water.

10 An oral chlorhexidine formulation as claimed in claim 8 or claim 9, comprising about 1.4-2 % wt. sodium fluoride.

11 An oral chlorhexidine formulation as claimed in any preceding claim, further comprising peppermint oil as a flavouring agent.

12 An oral chlorhexidine formulation as claimed in any preceding claim, comprising up to about 79 % wt. microcrystalline cellulose.

13 An oral chlorhexidine formulation as claimed in any preceding claim, comprising about 72-79 % wt. microcrystalline cellulose.

14 An oral chlorhexidine formulation as claimed in any preceding claim, comprising at least about 14 % wt. aspartame.

15 An oral chlorhexidine formulation as claimed in any preceding claim, comprising about 14-18 % wt. aspartame.

16 An oral chlorhexidine formulation as claimed in any preceding claim comprising about 2-5.7 polyoxyethylene glycol.

17 An oral chlorhexidine formulation comprising:

1.4 % wt. sodium fluoride

4.3 % wt. chlorhexidine acetate

14.3 % wt. aspartame

74.0-74.3 % wt. microcrystalline cellulose

5.7 % wt. polyethylene glycol 4000

0.0-0.3 % wt. peppermint oil.

18 An oral chlorhexidine formulation comprising:

2.0 % wt. sodium fluoride

5.6 % wt. chlorhexidine acetate

18.0 % wt. aspartame

72.4 % wt. microcrystalline cellulose

2.0 % wt. polyethylene glycol 4000.

19 A method of making an oral chlorhexidine formulation comprising mixing one or more chlorhexidine salts, one or more other optional active ingredients, and a non-active, chlorhexidine-compatible, water-soluble polyoxyethylene glycol with microcrystalline cellulose and thereafter milling the mixture to form a uniform powder.

20 A method as claimed in claim 19, further comprising compressing said powder to form tablets of the formulation

21 A method as claimed in claim 19 or claim 20, wherein the mixture of microcrystalline cellulose, chlorhexidine salt(s), other optional active ingredients and polyoxyethylene glycol is mixed with a mixture of microcrystalline cellulose and one or more other flavour-enhancing agents prior to milling.

22 A method of making an oral chlorhexidine formulation substantially as hereinbefore described in the example.

# INTERNATIONAL SEARCH REPORT

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A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K7/16 A61K31/155 A61K31/195

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
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| A | WO 01 74323 A (PORTMANN MARIE ;ALEXANDER STEPHEN EDWARD (GB); MCCONVILLE PETER SC) 11 October 2001 (2001-10-11) claim 7 --- | 1-22 |
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| A | WO 98 03154 A (WOWI LAB INC) 29 January 1998 (1998-01-29) example 6 --- | 1-22 |
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☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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